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# Batch Foaming of Amorphous Poly (DL-Lactic Acid) and Poly (Lactic Acid-co-Glycolic Acid) with Supercritical Carbon Dioxide: CO<sub>2</sub> Solubility, Intermolecular Interaction, Rheology and Morphology

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## 1. Introduction

Poly (lactic acid) (PLA) is a biobased aliphatic polyester prepared by condensation polymerization of lactic acid (2-hydroxy propionic acid) or ring opening polymerization of lactide in the presence of suitable catalysts (Garlotta, 2001; Lim et al., 2008). Lactic acid and lactide are chiral molecules (Figure 1). Lactic acid has two optical isomers, L-(+)-lactic acid or (S)-lactic acid and its mirror image D-(-)-lactic acid or (R)-lactic acid. Lactide is the cyclic di-ester of lactic acid and has three stereoisomers, i.e. meso-lactide, D-lactide and L-lactide. The majority of the commercially produced lactic acid is made by bacterial fermentation of carbohydrates. PLA has great potentials as an alternative to petroleum-based synthetic polymers and has been exploited as biodegradable thermoplastics for packaging and as FDA approved biomaterials for tissue engineering and drug delivery (Dorgan et al., 2001; Langer & Peppas, 2003).

PLA with the different ratio of L and D stereoisomers shows significantly different physical properties, for example PLA with high content of L-lactic acid (P<sub>L</sub>LA) ( e.g. greater than 90 %) is semicrystalline and PLA with more than 20% D-lactic acid content is amorphous (Tsuji, 2005; Lim et al., 2008). The crystallinity level of PLA decreases with D-lactic acid content and molecular weight. The copolymerization of lactic acid and glycolic acid has been used to tailor the biodegradability of the polymer. The rate of degradation of the polymers increases with the level of glycolic acid in the copolymer and decreases with molecular weight and crystallinity. Semicrystalline PLA can be converted into end-use products using conventional melt processing methods, including extrusion, injection molding, blow molding, casting, blown film, thermoforming, foaming, blending and fibre spinning (Lim et al., 2008). These processing methods require an elevated temperature of 10 to 20 °C above the melting point (ca. 175 °C) of the polymer. Therefore, they are not applicable when biologically active guest species are required to be incorporated into polymer host in situ to fabricate drug delivery and tissue engineering devices. Common techniques for the fabrication of 3-D porous tissue engineering scaffolds include solvent

casting/salt leaching (Lu et al., 2000; Murphy et al., 2002) and moulding/salt leaching (Hou et al., 2003; Sosnowski et al., 2006). In addition, for tissue engineering and drug delivery, double emulsion solvent evaporation method has been used to prepare microparticles/microspheres (Freitas et al., 2005; Jiang et al., 2005; Kim et al., 2006) and electrospinning has been used to prepare micro/nanofibres (Venugopal & Ramakrishna, 2005; You et al., 2006; Kim et al., 2010). However, organic solvents are often required in these fabrication approaches.

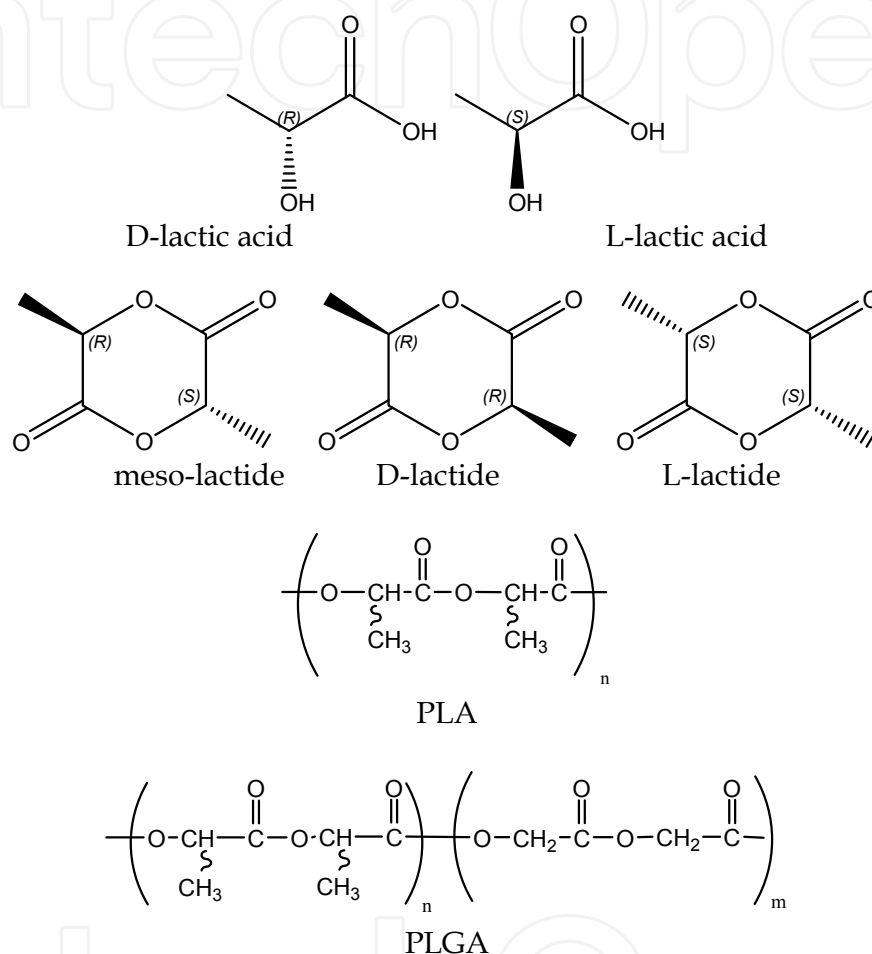


Fig. 1. Structures of lactic acid, lactide and PLA and PLGA

To overcome these limitations, carbon dioxide ( $\text{CO}_2$ ) has been successfully utilized as an efficient green plasticizer and foaming agent for the fabrication of 3-D porous biodegradable monolith scaffolds and microparticles using amorphous  $\text{P}_{\text{DLA}}$  and PLGA polymers at ambient temperatures (Mooney et al., 1996; Harris et al., 1998; Hile et al., 2000; Howdle et al., 2001; Davies et al., 2008). Supercritical carbon dioxide ( $\text{scCO}_2$ ) ( $T_c = 31.1^\circ\text{C}$ ,  $P_c = 73.8$  bar) has a unique combination of gas-like diffusivity and liquid-like density, which makes it a unique clean medium for polymer synthesis and polymer-processing (Cooper, 2001; Tomasko et al., 2003; Woods et al., 2004). In the supercritical foaming process, a small amount of  $\text{CO}_2$  dissolved into the polymers can dramatically reduce the glass transition temperature ( $T_g$ ) and the viscosity of the polymers, which make it possible to incorporate bioactive compounds into the polymer in situ at a low temperature thus to limit the loss of their activities. After the release of  $\text{CO}_2$  from the polymer, a porous structure can be formed.

In supercritical foaming process, control of pore structure is crucial because pore size, porosity and interconnectivity of scaffolds strongly influences cell growth behavior and drug release profile. The key for this is to control pore nucleation and growth which are mainly influenced by the amount of CO<sub>2</sub> dissolved in the polymer and the rate of CO<sub>2</sub> escaping from the polymer. Therefore, CO<sub>2</sub> solubility and polymer viscosity are two important aspects to study in order to control pore structure of scaffolds in supercritical foaming.

In this chapter, the recent studies on controlling the amorphous P<sub>DL</sub>LA and PLGA supercritical foaming process will be reviewed, particularly on the studies of the solubility of CO<sub>2</sub> in PLA and PLGA (Pini et al., 2007; Pini et al., 2008), the intermolecular interaction of CO<sub>2</sub> with PLA and PLGA (Tai et al., 2010), the rheological property of PLA and PLGA/CO<sub>2</sub> mixture (Tai et al., 2010), and the effects of processing conditions on the porous structures of the PLA and PLGA foams (Tai et al., 2007; Tai et al., 2007; White et al., 2011).

## 2. CO<sub>2</sub> solubility in PLA and PLGA

To control and optimise the supercritical foaming of amorphous PLA and PLGA polymers, it is important to study the solubility and diffusivity of the CO<sub>2</sub> in these biodegradable polymers. The solubility represents the amount of the CO<sub>2</sub> that can be dissolved in them at equilibrium conditions. CO<sub>2</sub> solubility in a wide range of polymers has been studied using gravimetric (Zhang et al., 2003; Oliveira et al., 2006) and spectroscopy (Duarte et al., 2005) methods. The sorption and swelling of PLA and PLGA polymers have been studied using different measurement techniques and also simulated using different mathematical modeling. These include a quartz crystal microbalance for the measurement and a dual-mode sorption model and Flory-Huggins equation for modelling used by Oliveira and coworkers (Oliveira et al., 2006; Oliveira et al., 2006); an external balance for the measurement and perturbed-hard-sphere-chain equation of state for modeling used by Elvassore and coworkers (Elvassore et al., 2005); and a pressure decay technique for the measurement and Sanchez-Lacombe equation of state for modeling used by Liu and coworkers (Liu & Tomasko, 2007). Oliveira *et al.* studied the solubility of CO<sub>2</sub> in PLA with two different L:D content, 80:20 (amorphous) and 98:2 (20 % crystallinity) (Oliveira et al., 2006). The experiments were performed between 30 and 50 °C and up to 50 bar. It was found that CO<sub>2</sub> is slightly more soluble in PLA 80:20 than in PLA 98:2. The solubility of CO<sub>2</sub> in both polymers shows the same trend, increasing with pressure and decreasing with temperature. Three models were used to correlate the experimental results, dual-mode sorption model, Flory-Huggins equation and an extended Flory-Huggins equation. Elvassore et al. applied a gravimetric method to obtain CO<sub>2</sub> absorption isotherms on three different polymers (PLGA 4852, PLGA 5446, and PLGA 5347) at 40 °C, which were then correlated using a perturbed-hard-sphere-chain equation of state (Elvassore et al., 2005). Liu and Tomasko used a pressure decay technique to measure CO<sub>2</sub> sorption isotherms of three polymers (PLGA 7525, PLGA 5050 and P<sub>DL</sub>LA homopolymer) at temperatures of 30, 40 and 60 °C and pressures up to 100 bar (Liu & Tomasko, 2007).

Pini et al. studied the solubility of amorphous P<sub>DL</sub>LA and PLGA polymers (Table 1) at 35 °C and up to 200 bar by measuring their sorption and swelling in CO<sub>2</sub> using a magnetic suspension microbalance and visualization method, and the Sanchez-Lacombe equation of state was used for correlating the experimental data (Pini et al., 2007; Pini et al., 2008). The P<sub>DL</sub>LA homopolymer shows the largest values of sorption and swelling (sorption and

fractional swelling up to 0.5 g CO<sub>2</sub>/g polymer and 0.68, respectively, at 200 bar), whereas the PLGA5050 has the lowest affinity to CO<sub>2</sub> (Figure 2). The sorption and swelling decrease with increasing the content of glycolic acid in PLGA copolymers. The Sanchez-Lacombe equation of state is the most widely used model to describe the solubility of CO<sub>2</sub> in polymers due to its simplicity, well-defined physical meaning, and the ability to extend available data to high temperature and pressures (Tomasko et al., 2003). Therefore, all data have been correlated by the Sanchez-Lacombe equation of state, demonstrating that this model is able to represent the actual behavior with reasonable accuracy using literature values for the pure component parameters and by fitting a single binary interaction parameter (Pini et al., 2008). CO<sub>2</sub> solubility and diffusivity are influenced by both the molecular structure (the interaction between CO<sub>2</sub> and polymer molecular chains) and the morphology (crystalline or amorphous, related with free volume) of polymers interested. Shieh and Lin suggested that the sorption process at or below P<sub>c</sub> was mainly driven by carbonyl groups and above P<sub>c</sub> by the degree of crystallinity such that the higher the degree of crystallinity, the lower CO<sub>2</sub> solubility in the polymer (Shieh & Lin, 2002). It is easy to understand that a strong interaction between CO<sub>2</sub> and polymer, and a low crystallinity (large free volume) of a polymer can lead to high gas solubility.

Polymers	Resources	Composition (LA:GA) <sup>a</sup>	M <sub>w</sub> <sup>b</sup> (KD)	PDI <sup>c</sup>	T <sub>g</sub> <sup>d</sup> (°C)
P <sub>DL</sub> LA 15K	Resomer	100:0	15	2.34	41.8
P <sub>DL</sub> LA 52K	Purac	100:0	52	1.87	46.9
PLGA 85:15	Lakeshore	85:15	77	1.70	48.6
PLGA 75:25	Resomer	75:25	72	1.75	50.4
PLGA 65:35	Lakeshore	65:35	52	1.69	49.1
PLGA 50:50	Resomer	50:50	53	1.59	47.0

<sup>a</sup> Copolymer composition: the mole ratio of lactic acid (LA) and glycolic acid (GA) in the copolymer; <sup>b</sup> Weight average molecular weight, determined by GPC; <sup>c</sup> Polydispersity, determined by GPC; <sup>d</sup> Glass transition temperature, determined by DSC.

Table 1. PLA and PLGA Polymers (Tai et al., 2010)

3. Intermolecular interaction of CO<sub>2</sub> with PLA and PLGA

Despite numerous studies of polymers with gases or supercritical fluids, there is a little molecular level information on interactions within these polymer systems. There was the general perception that polymer swelling or gas sorption is a purely physical phenomena till Kazarian *et al.* first studied the specific intermolecular interactions between CO<sub>2</sub> and polymers by FTIR and ATR-IR spectroscopy (Kazarian et al., 1996). It is suggested that the reduction of T<sub>g</sub> is a thermodynamic effect due to intermolecular interactions between CO<sub>2</sub> and the polymer and not simply a hydrostatic pressure effect (Tomasko et al., 2003). Nalawade *et al.* characterized polyesters, poly(ethylene glycol) and polyphenylene oxide by using a modified Fourier transform-infrared spectroscopy set-up under sub- and supercritical CO<sub>2</sub> conditions (Nalawade et al., 2006). Analysis of the corresponding spectra shows evidences of weak interaction (Lewis acid-base) between CO<sub>2</sub> and polymers. In particular, shifts to higher wavelengths of the maximum absorption of chain groups of the polymer and the modification of the absorption band of CO<sub>2</sub> represent a qualitative evidence of such interactions. In general, polymers with ether group display higher

interaction strength than polyesters. The chain flexibility aids dissolution of CO<sub>2</sub> in polymers and carbonyl or ether groups that are accessible in the backbone or on side chains can specifically interact with CO<sub>2</sub> (Kazarian et al., 1996; Tomasko et al., 2003; Nalawade et al., 2006).

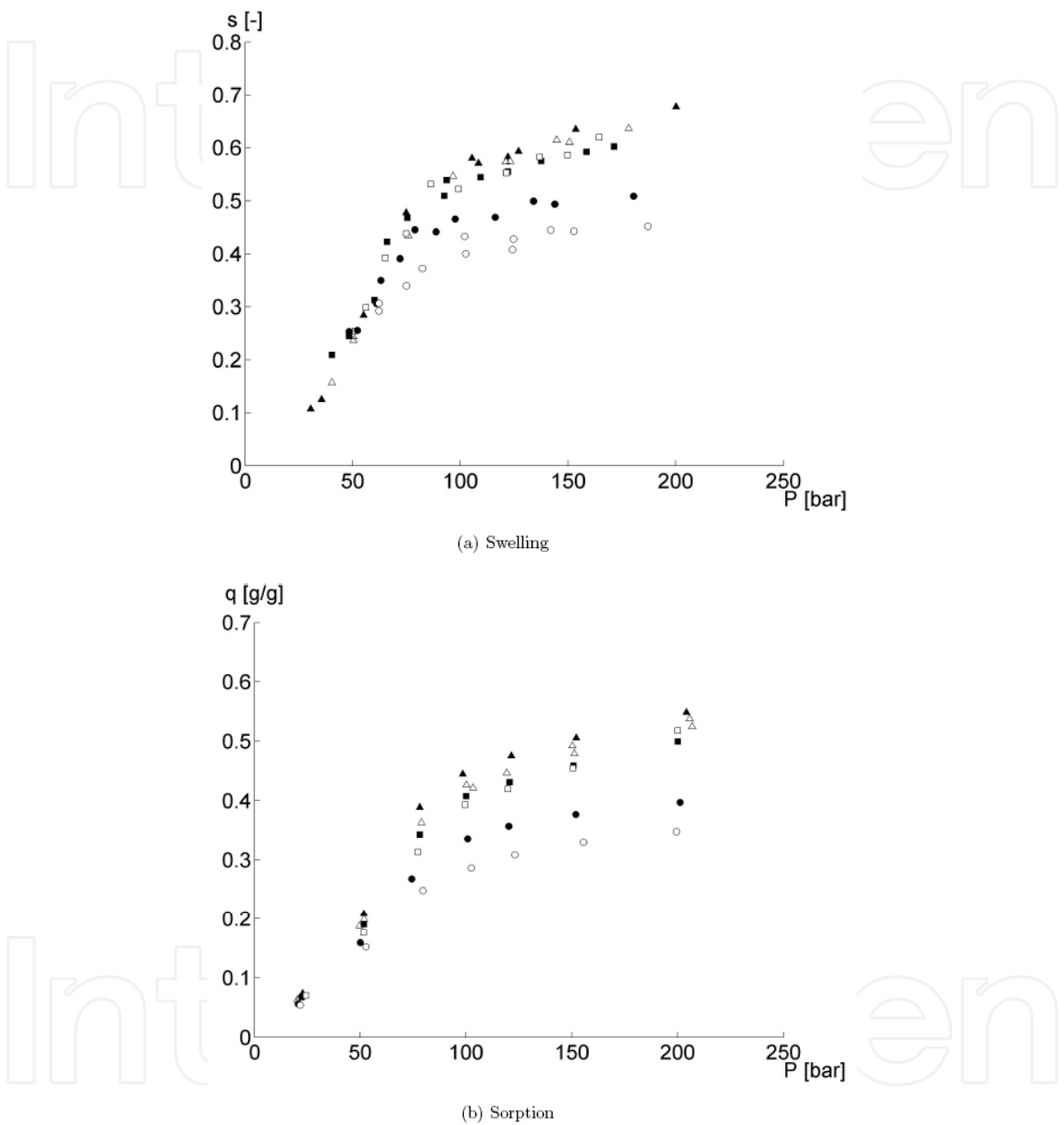


Fig. 2. Swelling and sorption isotherms at 35.0 °C as a function of pressure  $P$  for PLA15k (▲), PLA52k (Δ), PLGA8515 (■), PLGA7525 (□), PLGA6535 (●) and PLGA5050 (○). (a) Swelling  $s$  and (b) Sorption  $q$ . Reproduced with permission from (Pini et al., 2008)

Tai et al. adopted a high pressure attenuated total reflection Fourier transform infrared (ATR-IR) to investigate the interactions of CO<sub>2</sub> with PLA and PLGA polymers with the glycolic acid (GA) content in the copolymers as 15, 25, 35 and 50 % respectively (Table 1). Shifts and intensity changes of IR absorption bands of the polymers in the carbonyl region ( $\sim 1750$  cm<sup>-1</sup>) are indicative of the interaction on a qualitative level. The spectra for P<sub>DLLA</sub>



and PLGA polymers were recorded at 35 °C and 80 bar after soaking for 1 hour. The maximum absorptions in carbonyl region bands for all these polymers located at the similar position at ~1753.5 cm<sup>-1</sup> (Figure 3, b). In comparison with the spectra for the pure polymers (Figure 3, a), P<sub>DLLA</sub> had the largest shift (5.6 cm<sup>-1</sup>) and PLGA 5050 had the smallest shift (1.3 cm<sup>-1</sup>). This indicated that P<sub>DLLA</sub> had the greatest interaction with CO<sub>2</sub> and the interaction decreased with the increase of GA content in the polymers. This is in good agreement with the results obtained from the sorption and swelling studies, in which the solubility of CO<sub>2</sub> in PLGA copolymers was found to decreases with the increase in the glycolic acid content (Pini et al., 2007; Pini et al., 2008).

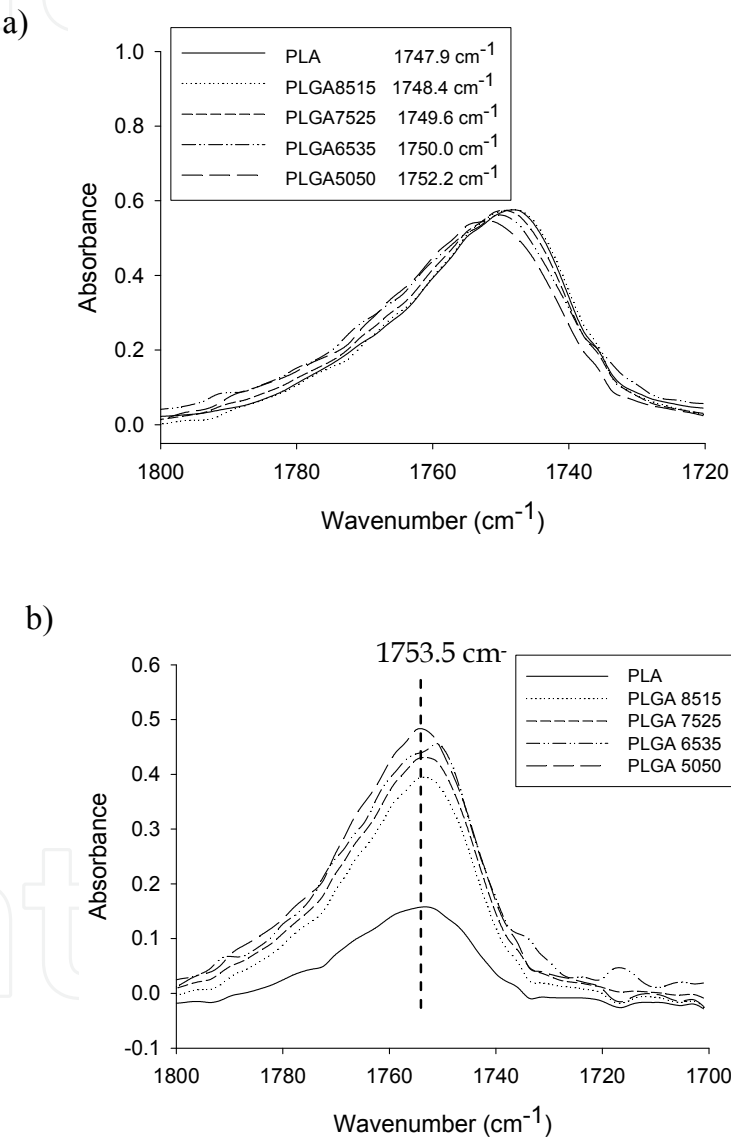


Fig. 3. FTIR spectra (carbonyl region bands) of P<sub>DLLA</sub> and PLGAs. (a) Sepctra for the pure polymers obtained in the absense of CO<sub>2</sub>, the absorbance bands in carbonyl region shift to high wavenumber with increasing GA content in the PLGA copolymers. (b) Spectra obtained for the polymers in the presence of CO<sub>2</sub> at 35 °C and 80 bar after soaking for 1 hour. Note, the maximum absorption in carbonyl region bands (picked by Omnic software) located at the position of ~1753.5 cm<sup>-1</sup>. Reproduced with permission from (Tai et al., 2010)

The interaction of polymers with CO<sub>2</sub> is dependent upon the chemical structure. The affinity of CO<sub>2</sub> with polyesters is largely due to the interaction of CO<sub>2</sub> molecules with the carbonyl group on the polymer chains. Lactic acid (LA) possesses an extra methyl group which could lead to at least two-opposing consequences. One is to increase the steric hindrance and then lower the interaction between the carbonyl group and the CO<sub>2</sub> molecules, whereas the other one is to increase the available free volume in the matrix due to the steric effect. The latter factor could have played a dominant role in determining the CO<sub>2</sub> behavior in PLGA polymers, leading to a higher solubility for PLGA with a high LA content.

#### 4. Rheology of PLA and PLGA

To process PLA polymers with conventional techniques, such as extrusion, injection molding, blow molding, casting, blown film, thermoforming and foaming, it is extremely important to understand the melt rheological behaviour of PLA which is highly dependent on temperature, molecular weight and shear rate (Lim et al., 2008). The melt rheology of semicrystalline P<sub>L</sub>LA has been studied at elevated temperatures above its melting point (Dorgan et al., 1999; Dorgan et al., 2000; Lehermeier & Dorgan, 2001; Palade et al., 2001; Dorgan et al., 2005). Cooper-White *et al.* studied the dynamic viscoelastic behavior of P<sub>L</sub>LA with molecular weights ranging from 2 to 360 kg/mol, over a broad range of reduced frequencies (approximately  $1 \times 10^{-3} \text{ s}^{-1}$  to  $1 \times 10^3 \text{ s}^{-1}$ ), using time-temperature superposition principle (Cooper-White & Mackay, 1999). The temperature range used was between 170 to 220 °C. Melts are shown to have a critical molecular weight of approximately 16 kg/mol, and an entanglement density of 0.16 mmol/cm<sup>3</sup> (at 25 °C). Fang *et al.* studied viscosities of two types of PLA resins (amorphous and semicrystalline) at 150 and 170 °C and at various shear rates (30, 50, 70, 90, 110, 130, and 150 rpm screw speeds) with a tube rheometer on an extruder (Fang & Hanna, 1999). The viscosity data was calculated from the pressure profiles and the volume flow rate. The effects of resin type, temperature and shear rate on melt viscosity were determined. Under the same processing conditions, semicrystalline PLA had a higher shear viscosity than amorphous PLA. As the temperature increased, the shear viscosity decreased for both types of PLA. The PLA melt was characterized as a pseudoplastic, non-Newtonian fluid. Dorgan *et al.* also studied the melt rheology of PLA by measuring master curves of polymers. The effects of variable L-content (Palade et al., 2001; Dorgan et al., 2005), entanglement and chain architecture (Dorgan et al., 1999), linear and star polymer chain architecture (Dorgan et al., 2000) and blending chain architectures (Lehermeier & Dorgan, 2001) on the rheological property of PLA were investigated. The dynamic frequency sweeps were performed at 180 °C to obtain zero shear viscosity data for a linear and a branched PLA (Dorgan et al., 2000). Longer relaxation times for the branched material, compared to the linear material, manifests itself as a higher zero shear rate viscosity. However, the branched material shear thins more strongly, resulting in a lower value of viscosity at high shear rate. Isothermal frequency sweeps were also performed at a wide range of temperatures from (56 to 180 °C) for semicrystalline P<sub>L</sub>LA and amorphous P<sub>DL</sub>LA (Dorgan et al., 2005). For all compositions of PLA investigated, the weight average molecular weights were within the range of 10<sup>5</sup>-10<sup>6</sup> g/mol.

CO<sub>2</sub> has been used in gas assisted extrusion process to reduce the glass transition temperature and the viscosity of the polymer, also to increase the miscibility of the different polymers in blending to form polymer composites (Garlotta, 2001; Lim et al., 2008).



However, there are very few studies about extrusion foaming of PLA (Reignier et al., 2007; Mihai et al., 2010). Mihai et al. studied the rheology and extrusion foaming of chain-branched PLA at a temperature between 180 °C to 200 °C (Mihai et al., 2010). Two PLA grades, an amorphous and a semicrystalline one, were branched using a multifunctional styrene-acrylic-epoxy copolymer. The branching of PLA and its foaming were achieved in one-step extrusion process. CO<sub>2</sub> up to 9% was used to obtain foams from the two PLA branched using chain-extender contents up to 2%. The foams were investigated with respect to their shear and elongational behavior, crystallinity, morphology, and density. The addition of the chain-extender led to an increase in complex viscosity, elasticity, elongational viscosity, and in the manifestation of the strain-hardening phenomena. Differences in foaming behavior were attributed to crystallites formation during the foaming process. The rheological and structural changes associated with PLA chain-extension lowered the achieved crystallinity but slightly improved the foamability at low CO<sub>2</sub> content. Corre et al studied the batch foaming of modified PLA with scCO<sub>2</sub> (Corre et al., 2011). Improvement of the melt viscosity and elasticity was achieved by the use of an epoxy additive during a reactive extrusion process. Rheological characterizations confirmed an increase of the melt strength due to this chain extension process. Foaming was then performed on the neat and modified PLAs using a batch process with scCO<sub>2</sub> as blowing agent using the saturation temperature of 165 °C and pressure ranging from 96 to 142 bar. Depending on the foaming parameters, foams with a cellular structure ranging from macro scale to micro scale have been obtained.

The viscosity of polymer/CO<sub>2</sub> mixture plays an important role for the control of porous structures in CO<sub>2</sub> foaming process. The dissolved CO<sub>2</sub> in the polymers reduces the viscosity and T<sub>g</sub> of the polymers dramatically (Tomasko et al., 2003; Woods et al., 2004). These reductions are closely related to the solubility of CO<sub>2</sub> in the polymers. The higher the solubility of CO<sub>2</sub> in a polymer, the higher is the reduction in the viscosity and the glass transition temperature (Nalawade et al., 2006). To study the rheological property of PLA in the presence of CO<sub>2</sub>, high pressure rheometer or high pressure viscometer are required. There are several studies on the viscosity reduction of polymer melts or fluid samples under CO<sub>2</sub> using high pressure concentric cylinder rotational viscometer (Flichy et al., 2003), high pressure slit die (Royer et al., 2001) and capillary viscometer (Qin et al., 2005), and high pressure magnetically levitated sphere rheometer (Royer et al., 2002). Tai et al. studied the rheological properties of amorphous P<sub>D</sub>LLA and PLGA polymers in the presence and absence of CO<sub>2</sub> using a parallel plate rheometer (Tai et al., 2010). The viscosity curves of P<sub>D</sub>LLA, PLGA 8515 and PLGA 6535 were recorded at 35 °C and 100 bar after CO<sub>2</sub> saturated the polymers (soaking for 24 hours). It was found that the viscosity curves (i.e., shear viscosity versus shear rate) of polymer/CO<sub>2</sub> mixtures were similar in shape to those of pure polymers (Figure 4, a and b). The shear thinning phenomenon was observed for all the polymers, which is important information for extrusion and injection processing of the polymers. The comparison of zero viscosity data for the polymers indicated that the dissolved CO<sub>2</sub> (ca. 25-30 wt %) lowered the viscosity of P<sub>D</sub>LLA and PLGA at 35 °C to the similar level for the pure polymers at a high temperature of 140 °C (Figure 4, c). Moreover, a greater viscosity reduction for P<sub>D</sub>LLA was observed comparing to PLGAs. These rheological data also demonstrated that the interactions of CO<sub>2</sub> with amorphous P<sub>D</sub>LLA and PLGA polymers decrease with increasing GA content in the polymers.

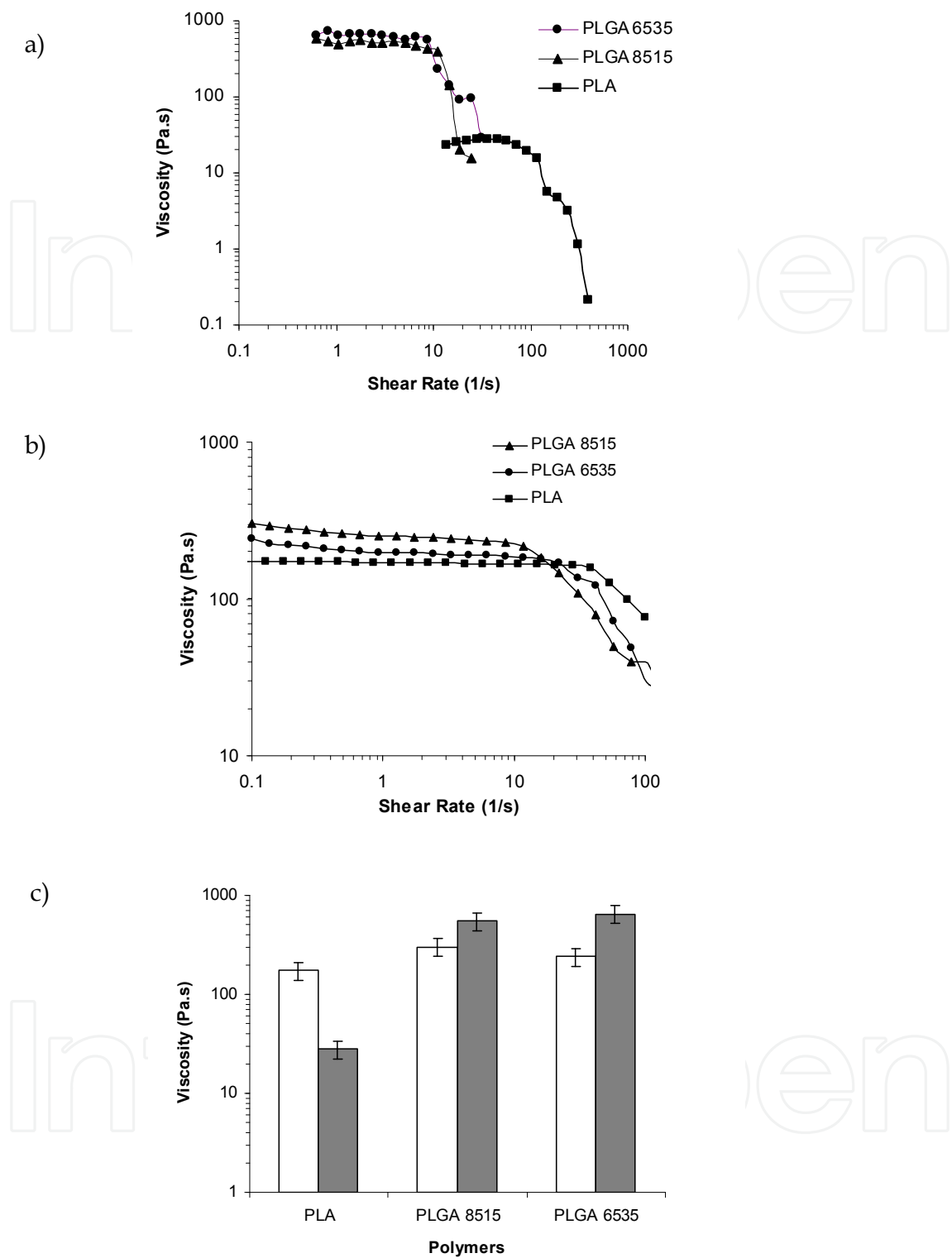


Fig. 4. Shear viscosity of P<sub>DL</sub>LA, PLGA 8515 and PLGA 6535 with and without CO<sub>2</sub>. (a) Flow curves for CO<sub>2</sub>-plastitized polymers at 35 °C and 100 bar after soaking for 24 hours; (b) Flow curves for polymer melts at 140 °C and atmosphere pressure; (c) Comparison of the zero viscosities of the polymers at 140 °C and atmosphere (white bars) with those at 35 °C and 100 bar CO<sub>2</sub> pressure (grey bars). Reproduced with permission from (Tai et al., 2010)

## 5. Morphology of supercritical foamed PLA and PLGA scaffolds

Tissue engineering scaffolds require a controlled pore size and structure to host tissue formation and drug release. The chemical composition of the polymers and the morphology (pore size, porosity and interconnectivity) of the porous scaffolds are crucial because these parameters influence cell filtration, migration, nutrient exchange, degradation and drug release rate. CO<sub>2</sub> batch foaming process was used to fabricate foamed scaffolds in which the escape of CO<sub>2</sub> from a plasticized polymer melt generates gas bubbles that shape the developing pores. Mooney et al formed PLGA scaffolds (a mole ratio of lactic acid and glycolic acid (L/G) was 50:50) by CO<sub>2</sub> pressure quenching method at 20-23 °C and 55 bar (Mooney et al., 1996). Pishko et al. produced PLGA (L/G ratio as 80:20 and 65:35) scaffolds *via* CO<sub>2</sub> pressure quenching method using a water-in-solvent emulsion (aqueous protein phase and organic polymer solution phase) at conditions in the supercritical region (35 °C, 80 bar) (Hile et al., 2000; Hile & Pishko, 2004). Howdle and Shakesheff developed a single step scCO<sub>2</sub> foaming process using polymer powder samples to generate porous scaffolds at high pressure (170-230 bar) and short soaking time (0.5-2 hours) with a controlled venting rate (venting time between 2 minutes and 2 hours) at 35 °C (Howdle et al., 2001). The produced scaffolds with an interconnected porous structure have been used for growth factor and gene delivery. For example, bone morphogenetic protein 2 (BMP-2) has been encapsulated into P<sub>DLLA</sub> scaffolds for bone tissue engineering by this supercritical fluid mixing and foaming (Yang et al., 2004). Bone formation was observed due to the release of the osteoinductive protein BMP-2 from P<sub>DLLA</sub> scaffolds both in vitro and in vivo (Yang et al., 2004; Yang et al., 2006). These scaffolds have also been used to study adenoviral gene transfer into primary human bone marrow osteoprogenitor cells (Howard et al., 2002; Partridge et al., 2002). Polyamidoamine polymer (PAA)/DNA complexes has been incorporated into supercritical P<sub>DLLA</sub> scaffold, exhibiting a slow release and extended gene expression profile (Heyde et al., 2007).

The process of CO<sub>2</sub> batch foaming involves a simultaneous change in phase in the CO<sub>2</sub> and the polymer, resulting in rapid expansion of a surface area and changes in polymer rheological properties. Hence, the process is difficult to control with respect to the desired final pore size and structure. Tai et al. performed a detailed study of the effects of polymer chemical composition, molecular weight and batch foaming conditions on final scaffold characteristics (Tai et al., 2007; White et al., 2011). A series of amorphous P<sub>DLLA</sub> and PLGA polymers with various molecular weights (from 13 KD to 96 KD) and/or chemical compositions (the mole percentage of glycolic acid in the polymers was 0, 15, 25, 35 and 50 respectively) were employed. Processing parameters under investigation were temperature (from 5 to 55 °C), pressure (from 60 to 230 bar), soaking time and venting rate. The results demonstrated that the pore size and structure of the supercritical P<sub>DLLA</sub> and PLGA scaffolds can be tailored by careful control of the processing conditions. A higher pressure and a longer soaking time allowed more CO<sub>2</sub> molecules to diffuse into the polymer matrix, leading to a higher nucleation density and hence the production of smaller pores. Higher temperatures produced foams with larger pores because increased diffusion rates facilitated pore growth. In addition, reducing the rate of depressurization allowed a longer period for pore growth and therefore larger pores were formed than with rapid depressurization. The pore size of scaffolds also decreased with increasing glycolic acid content in the PLGA copolymers (Figure 5).

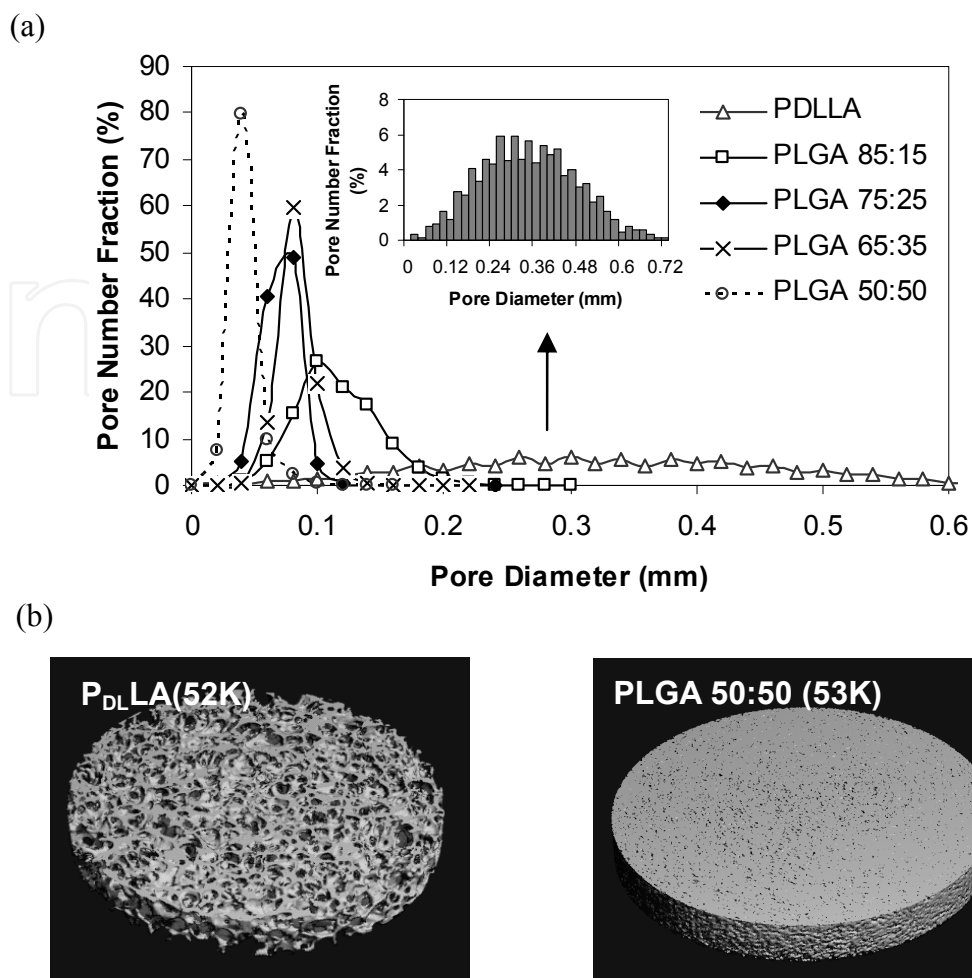


Fig. 5. Scaffolds fabricated with P<sub>DL</sub>LA(52K), PLGA 85:15(77K), PLGA 75:25(72K), PLGA 65:35(52K), and PLGA 50:50(53K) polymers. (a) pore size distribution determined by Micro CT; (b) Micro CT 3-D images. Processing conditions: T = 35 °C, P = 230 bar, FT = 20 minutes, ST = 60 minutes, VT = 60 minutes. Reproduced with permission from (Tai et al., 2007)

## 6. Conclusion

Batch foaming of amorphous poly (DL-lactic acid) and poly (lactic acid-co-glycolic acid) with supercritical carbon dioxide is a solvent-free approach and without the need of an elevated temperature for the fabrication of 3-D porous scaffolds. CO<sub>2</sub> sorption and swelling isotherms at 35 °C and up to 200 bar on a variety of homo- and copolymers of lactic and glycolic acids (glycolic acid content as 0, 15, 25, 35 and 50 % respectively) have been studied. A high pressure attenuated total reflection Fourier transform infrared (ATR-IR) have been successfully used to study the interactions of CO<sub>2</sub> with these polymers. Shifts of the maximum absorption of carbonyl groups (C=O) of the polymers and the absorption intensity changes of both carbonyl and CO<sub>2</sub> bands represent such interactions. The viscosity of CO<sub>2</sub>-plasticised polymers has been measured directly using high pressure parallel plate rheometer at 35 °C and 100 bar and the results were compared with the viscosity of the polymer melts at 140 °C. All data demonstrated that the interactions of CO<sub>2</sub> with PLGA polymers decreased with the increase of GA contents in the copolymers. These

investigations provided fundamental understandings on the control of scCO<sub>2</sub> foaming process for the fabrication of P<sub>DLLA</sub> and PLGA porous scaffolds. Moreover, the experiments have been performed to tailor the pore size and structure of the P<sub>DLLA</sub> and PLGA porous scaffolds by altering the processing conditions. The results demonstrated that a higher pressure and a longer soaking time allowed more CO<sub>2</sub> molecules to diffuse into the polymer matrix, leading to a higher nucleation density and hence the production of smaller pores. Higher temperatures produced foams with larger pores because increased diffusion rates facilitated pore growth. In addition, reducing the rate of depressurization allowed a longer period for pore growth and therefore larger pores were formed than with rapid depressurization. The pore size of scaffolds also decreased with increasing glycolic acid content in the PLGA copolymers. These findings empower the definition of scCO<sub>2</sub> batch foaming conditions to tailor the pore size and structure of scaffolds for potential application as controlled release devices for growth factor delivery in Tissue Engineering.

## 7. References

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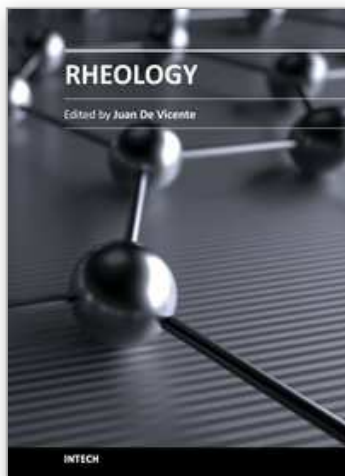
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